APPLICANTS: Zhang et al. **DOCKET NO: ISPH-0803 (ISIS.068C1)**
SERIAL NO: 10/728,509

REMARKS

Claims 1-14 were pending. Upon entry of this Amendment, claims 1-9 and 11-14 will be pending. Claim 10 is canceled herein without prejudice to its presentation in another application.

Claim 1 is amended herein to remove functional limitation language. Claim 14 is amended to specify inhibition is "in vitro." No new matter has been added to the claims.

The claim amendments and cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. Applicant reserves the right to file subsequent applications claiming the canceled subject matter.

INFORMATION DISCLOSURE STATEMENTS

The Examiner notes that the information disclosure statements submitted 12/5/03 and 10/31/05 failed to comply with 37 CFR §1.98(a)(2). Applicants respectfully submit the information disclosure statement filed 10/31/05 cites only a singe U.S. patent reference. In accordance with §1.98(a)(2)(i), Applicants are not required to submit a copy of this reference since the instant application was filed after June 30, 2003. In regard to the information disclosure statement filed 12/5/03, each reference was provided in a parent application, U.S. Application Serial No. 09/908,147, filed July 17, 2001. Thus, in accordance with §1.98(d), Applicants are not required to submit copies of these references in connection with the instant application.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-14 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written descriptive support in the application. The Office Action alleges the specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus claimed. The Office Action states that the specification discloses antisense oligonucleotides 20 nucleotides in length and fully complementary to SEQ ID NO: 17. Thus, the Office Action concludes that the specification and claims do not adequately teach a representative number of species for the broad genus claimed. Applicants respectfully traverse this rejection.

The test for sufficiency of support under the written description requirement was provided by the Court in *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991), which stated, "Although [the applicant] does not have to describe exactly the subject matter claimed...the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (citations omitted). The decision rendered in *Vas-Cath, Inc. v. Mahurkar* was affirmed in *Falkner v. Inglis*, No. 05-1324 (US Court of Appeals for the Federal Circuit, May 26, 2006), which concluded that:

> (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of the known structure.

The decision by the Federal Circuit in *Falkner v. Inglis* is in accordance with prior case law, including *Lizard Tech, Inc. v. Earth Resource Mapping, PTY, Inc.* 424 F.3d 1336, 1345 (Fed. Cir. 2005) and *Union Oil Co. v. Atlantic Richfield Co.* 208 F.3d 989, 997 (Fed. Cir. 2000), which concluded, "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language."

While the instant application does not provide a listing of each and every sequence encompassed by the pending claims, Applicants are still in compliance with the written description requirement. As noted above, there is no requirement to provide explicit examples covering the full scope of the claims. Applicants have provided a number of explicit examples of antisense oligonucleotides falling within the genus claimed and have provided sufficient disclosure to describe the remaining oligonucleotides of the claimed genus, such that one of ordinary skill in the art would recognize Applicants to be in possession of the claimed invention.

Whether the written description requirement is met is a question of fact, determined on a case-by-case basis. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil V. Atlantic Richfield Co.* Given the "nature" of antisense technology, one of ordinary skill in the art

need only be provided with a target sequence against which to design antisense oligonucleotides, a description of how to make and use the antisense oligonucleotides, length limitations and chemical modifications in order to conclude that Applicants were in possession of the invention as instantly claimed. The instant specification thoroughly discloses each of these aspects. The description provided by the instant application imparts a wide breadth of knowledge on antisense compounds, including antisense oligonucleotides, targeted to BCL2-associated X protein (SEQ ID NO: 17). For example, the specification describes targeting compounds to a specific target nucleic acid and antisense compounds specifically hybridizable with a target nucleic acid (see, for example, pages 5-6 and 8-9 of the specification). The specification further describes length limitations for antisense compounds, including 8 to 50 (see page 12 of the specification). The specification further provides numerous oligonucleotide modifications (see pages 12-21 of the specification). Examples 1-5 provide a description for synthesis of oligonucleotides, while Examples 7 and 8 describe the synthesis and analysis of antisense compounds using a 96-well plate format. In addition, specific antisense oligonucleotides targeted to the 3'UTR of SEQ ID NO: 17 are exemplified in Example 15.

Taken together, the instant application provides a thorough description of the antisense oligonucleotides currently claimed and provides a number of specific sequences falling within the scope of the claims. As noted above, Applicants need not provide each and every sequence of the antisense oligonucleotides covered by the instant claims. In fact, "the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification" (*Falkner v. Inglis*) and is discouraged by the Patent Office as it only serves to increase application page numbers and overload sequence databases.

Furthermore, as detailed in the MPEP, the initial burden of proof in establishing whether the claims are supported by an adequate written description falls upon the Examiner. "The description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption" (MPEP 2163.04 and *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). The Examiner has not provided any evidence to show that one of skill in the art, given the disclosure (described in detail above), would not recognize Applicants to be in possession of the claimed compounds and

methods.

Accordingly, Applicants respectfully request withdrawal of the written description rejection under 35 U.S.C. §112, first paragraph.

Claim 14 is rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. Without agreeing with the Examiner's position and solely to advance prosecution of the instant application, Applicants have amended claim 14 herein recite that inhibition of BCL2-associated X protein occurs in vitro.

Accordingly, Applicants respectfully request withdrawal of the enablement ejection under 35 U.S.C. §112, first paragraph.

REJECTIONS UNDER 35 U.S.C. §102/103

Claims 1, 2, 10, 11 and 13 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as allegedly being obvious over Zhou et al. (1998, J. Biol. Chem. 273(19):11930-11936).

Claims 1, 2, 10, 11 and 13 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as allegedly being obvious over Apte et al. (1995, Genomics 16:592-594).

The Office Action alleges Zhou et al. and Apte et al. each teach antisense oligonucleotides between 8 and 50 nucleobases in length that specifically target the 3'UTR of SEQ ID NO: 17. Applicants respectfully traverse these rejections.

Contrary to the Examiner's assertions, neither Apte et al. nor Zhou et al. teach any antisense oligonucleotides which target and/or specifically hybridize with instant SEQ ID NO: 17. Sequence alignments of the primers disclosed by the cited references and SEQ ID NO: 17 demonstrated that none of the primers target or specifically hybridize with SEQ ID NO: 17. Since Zhou et al. and Apte et al. do not teach each and every limitation of the pending claims, the references do not anticipate, or render obvious, the pending claims.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §102 and/or §103.

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REJECTIONS UNDER 35 U.S.C. §103(a)

Claims 1-14 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Zhou et al. and Apte et al. (as applied to claims 1, 2, 10 and 13 above) in view of Korsmeyer (6,500,626) and further in view of Milner et al. (1997, Nature Biotech. 15:537-541) and McKay (6,133,246). The Office Action states Zhou et al. and Apte et al. do not teach inhibition of expression of SEQ ID NO: 17, the incorporation of oligonucleotide modifications, chimeric antisense oligonucleotides or colloidal dispersion systems. The Office Action alleges Korsmeyer teaches inhibition of expression of SEQ ID NO: 17 using antisense oligonucleotides; Milner et al. teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit expression of a target sequence; and McKay et al. teach colloidal dispersion compositions comprising antisense oligonucleotides. The Office Action concludes it would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit expression of SEQ ID NO: 17 as instantly claimed based on the teachings of the cited references. Applicants respectfully traverse this rejection.

As presented above, neither Zhou et al. nor Apte et al. teach any compounds targeted to or specifically hybridizable with SEQ ID NO: 17, nor do they teach any compounds targeted to or specifically hybridizable with the 3'UTR of SEQ ID NO: 17. Korsmeyer, Milner et al. and McKay et al. do not cure the deficiencies of Zhou et al. and Apte et al. None of the cited references, alone or in combination, teach each and every limitation of the pending claims. Thus, the Office has failed to establish a *prima facie* case of obviousness.

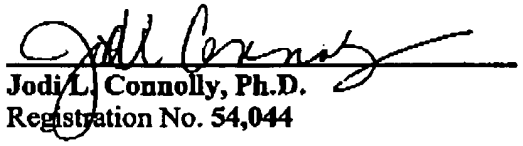
Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

It is believed that no fee is due with this response. However, if a fee is due, the Commissioner is hereby entitled to charge the fee to Deposit Account 50-0252, referencing the above named application.

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and reconsideration of the claims

is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the Agent for Applicant listed below to discuss any outstanding matters.

Respectfully submitted,



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